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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/394,230	09/13/1999	KEVIN L. GUNDERSON	393382001600	3919

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EXAMINER	
FORMAN, BETTY J	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/394,230	GUNDERSON ET AL.	
	Examiner	Art Unit	
	BJ Forman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 16 00 04 02
4) ☒ Interview Summary (PTO-413) Paper No(s). 0603
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

FINAL ACTION

1. This action is in response to papers filed 22 April 2003 in which claims 1, 12 and 14 were amended. All of the amendments have been thoroughly reviewed and entered. The previous objections and rejections in the Office Action dated 16 January 2003 are withdrawn in view of the amendments. All of the arguments have been thoroughly reviewed but are deemed moot in view of the amendments, withdrawn rejections and new grounds for rejection.

New grounds for rejection are discussed.

Claims 1-18 are under prosecution.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cantor et al. (U.S. Patent No. 5,631,134, filed 5 June 1995) in view of Southern (U.S. Patent No. 5,700,637, filed 19 April 1994) and Huang et al (U.S. Patent No. 6,287,778, filed 19 October 1999) and/or Lipshutz et al (U.S. Patent No. 6,300,063, filed 29 November 1995).

Regarding Claim 1, Cantor et al. teach a method of determining the presence of a mutation in a target polynucleotide comprising the steps of providing a polynucleotide probe array wherein each probe comprises a double strand region and a single stranded n-mer overhang region; hybridizing a target polynucleotide to said overhangs in the array to generate a target hybridization pattern; and determining the presence of a mutation in the target polynucleotide by analyzing hybridization patterns (Column 8, lines 1-12) wherein the probes are designed to identify mutations (Column 4, lines 5-8) wherein the a single stranded n-mer overhang region is "preferably" about 4 to 20 nucleotides in length (Column 5, lines 60-65) and wherein the set of probes on the array comprises every possible n-mer (Column 6, lines 3-5). Cantor et al. do not teach hybridizing a reference polynucleotide to a second array and determining the presence of a mutation by comparing the reference and target hybridization patterns. However, the comparison of reference and target hybridization patterns to determine the presence of a mutation was known and routinely practiced in the art at the time the claimed invention was made. Specifically, Southern teaches a similar method for determining the presence of a mutation in a target polynucleotide comprising hybridizing a target polynucleotide to array and a reference polynucleotide to a second array (Column 7,lines 10-31) and determining the presence of a mutation by comparing reference and target hybridization patterns without sequencing the target polynucleotide (Column 3, lines 58-62) wherein the n-mer arrays are complete n-mer arrays (Column 6, lines 8-27). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the complete n-mer hybridization detection and analysis of Cantor et al. with the complete n-mer hybridization comparison analysis of Southern whereby comparing hybridization patterns reveals differences between the target and reference and eliminates the need for sequencing the target sequence (Column 3, lines 52-62) and wherein the hybridizations are extremely sensitive because complete n-mer hybridizations are performed under highly stringent conditions to discriminate between single mismatch sequences as

taught by Southern (Column 10, line 57-67-Column 11, line 4) for the expected benefits of identifying mutations accurately, efficiently and economically i.e. identifying mutations under highly stringent conditions without the time and labor consuming sequencing reactions.

Cantor et al and Southern do not teach the arrays comprise perfect match and mismatch probes wherein mutation determination is via normalizing hybridization intensities utilizing the mismatch and perfect match probes. However, Huang et al teach a very similar method comprising hybridizing target polynucleotides to double-stranded probes on an array (Column 10, lines 6-22, especially line 14) wherein normalization intensity differences comprises dividing the perfect match hybridization intensity by the hybridization intensity for mismatch probes (Column 11, lines 16-35). Lipshutz et al also teach a similar method comprising hybridizing target polynucleotides to probes having an overhang (Column 5,lines 21-24) on an array comprising perfect match and mismatch probes (Example 2, Column 12, lines 15-32) wherein normalization intensity differences comprises dividing the perfect match hybridization intensity by the hybridization intensity for mismatch probes (Column 9, line 36-Column 10, line 56). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the normalization of Huang et al and/or Lipshutz et al to the mutation detection of Cantor et al and Southern to thereby unambiguously genotype each polymorphic locus as taught by Huang et al (Column 19, lines 26-56).

Regarding Claim 2, Cantor et al. teach the hybridized polynucleotide is ligated to the probe (Column 8, lines 8-9).

Regarding Claim 3, Cantor et al. teach the hybridized polynucleotide is ligated to the probe (Column 8, lines 8-9). Cantor et al. do not discuss the reference polynucleotide. However, reference polynucleotides were known to one of ordinary skill in the art as discussed above and the skilled practitioner would have known that for comparison purposes, a target and reference polynucleotide would be treated equally i.e. ligated to the probe.

Regarding Claim 4, Cantor et al. teach the overhangs have free 5' ends (Column 12, lines 46-49 and Fig. 1B).

Regarding Claim 5, Cantor et al. teach the overhangs have free 3' ends (Column 12, lines 38-45 and Fig. 1A).

Regarding Claim 6, Cantor et al. teach the n-mer comprises from about 4 to 50 nucleotides (Column 12, lines 57-60).

Regarding Claims 7-9, Cantor et al. teach the mutation is a single nucleotide mutation (Column 10, lines 38-40). Cantor et al. do not teach the single nucleotide mutation is a substitution (Claim 7), a deletion (Claim 8) and an insertion (Claim 9). However, one skilled in the art at the time the claimed invention was made would have known that the single nucleotide mutations taught by Cantor et al. include the claimed substitution, deletion and insertion mutations.

Regarding Claim 10, Cantor et al teach the method wherein single nucleotide mutations are identified wherein the identification quickly, efficiently and easily detects inherited mutations which cause disease and DNA depended phenotype and somatic variations (Column 10, lines 38-45). Cantor et al. do not teach the target polynucleotide is selected from the recited sequences. However, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Cantor et al. with the teachings of Cantor et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to apply the mutation detection teaching of Cantor et al. to sequences known to contain single nucleotide mutations for the obvious benefit of detecting clinically relevant mutations quickly, efficiently and easily as taught by Cantor et al.

Regarding Claim 11, Cantor et al. do not teach parallel arrays. However, Southern teaches the similar method wherein the arrays are arranged in parallel i.e. stripes (Column 7, lines 12-22) whereby numerous sequence variations are analyzed simultaneously wherein each

stripe corresponds to a different sequence variation. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the single array of Cantor et al. with the parallel arrays (i.e. strips) of Southern for the expected benefit of analyzing numerous mutations simultaneously as taught by Southern (Column 7, lines 23-26).

Regarding Claim 12, Cantor et al. teach a method of determining relatedness two or more polynucleotides comprising the steps of providing a polynucleotide probe array wherein each probe comprises a double stranded region and a single stranded n-mer overhang region such that the over hangs in each array constitute a complete set of n-mers; hybridizing a target polynucleotide to said overhangs in the array to generate a hybridization pattern and analyzing the hybridization patterns (Column 8, lines 1-10) wherein the a single stranded n-mer overhang region is "preferably" about 4 to 20 nucleotides in length (Column 5, lines 60-65) and wherein the set of probes on the array comprises every possible n-mer (Column 6, lines 3-5). Cantor et al. do not teach the method comprising two identical arrays wherein the target polynucleotide is hybridized to one array and a second target polynucleotide is hybridized to a second array. However, the comparison of hybridization patterns to determine if two or more sequences are identical was known and routinely practiced in the art at the time the claimed invention was made. Specifically, Southern teaches a similar method for determining whether two or more target polynucleotides are identical comprising providing at least two identical polynucleotide probe arrays; hybridizing a first polynucleotide to one array stripe and a second polynucleotide to a second array stripe (Column 7,lines 10-31) and comparing the first and second hybridization patterns without sequencing the target polynucleotide (Column 3, lines 58-62). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the complete n-mer hybridization detection and analysis of Cantor et al. with the complete n-mer hybridization comparison analysis of Southern whereby comparing hybridization patterns reveals differences between sequences and eliminates the need for sequencing the sequences (Column 3, lines 52-62) and wherein the hybridizations are

extremely sensitive because complete n-mer hybridizations are performed under highly stringent conditions which discriminate between single mismatch sequences (Column 10, line 57-67-Column 11, line 4) for the expected benefits of determining sequence similarity accurately, efficiently and economically i.e. determining sequence similarity under highly stringent conditions without the time and labor consuming sequencing reactions.

Cantor et al and Southern do not teach the arrays comprise perfect match and mismatch probes wherein mutation determination is via normalizing hybridization intensities utilizing the mismatch and perfect match probes. However, Huang et al teach a very similar method comprising hybridizing target polynucleotides to double-stranded probes on an array (Column 10, lines 6-22, especially line 14) wherein normalization intensity differences comprises dividing the perfect match hybridization intensity by the hybridization intensity for mismatch probes (Column 11, lines 16-35). Lipshutz et al also teach a similar method comprising hybridizing target polynucleotides to probes having an overhang (Column 5,lines 21-24) on an array comprising perfect match and mismatch probes (Example 2, Column 12, lines 15-32) wherein normalization intensity differences comprises dividing the perfect match hybridization intensity by the hybridization intensity for mismatch probes (Column 9, line 36-Column 10, line 56). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the normalization of Huang et al and/or Lipshutz et al to the mutation detection of Cantor et al and Southern to thereby unambiguously genotype each polymorphic locus as taught by Huang et al (Column 19, lines 26-56).

Regarding Claim 13, Cantor et al. teach the hybridized polynucleotide is ligated to the probe (Column 8, lines 8-9).

Regarding Claim 14, Cantor et al. teach the hybridized polynucleotide is ligated to the probe (Column 8, lines 8-9). Cantor et al. do not discuss the reference polynucleotide. However, reference polynucleotides were known to one of ordinary skill in the art as discussed

above and the skilled practitioner would have known that for comparison purposes, a target and reference polynucleotide would be treated equally i.e. ligated to the probe.

Regarding Claim 15, Cantor et al. teach the overhangs have free 5' ends (Column 12, lines 46-49 and Fig. 1B).

Regarding Claim 16, Cantor et al. teach the overhangs have free 3' ends (Column 12, lines 38-45 and Fig. 1A).

Regarding Claim 17, Cantor et al. teach the n-mer comprises from about 4 to 50 nucleotides (Column 12, lines 57-60).

Regarding Claim 18, Cantor et al. do not teach parallel arrays. However, Southern teaches the similar method wherein the arrays are arranged in parallel i.e. stripes (Column 7, lines 12-22) whereby numerous sequence variations are analyzed simultaneously wherein each stripe corresponds to a different sequence variation. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the single array of Cantor et al. with the parallel arrays (i.e. strips) of Southern for the expected benefit of analyzing numerous mutations simultaneously as taught by Southern (Column 7, lines 23-26).

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
Patent Examiner
Art Unit: 1634
June 25, 2003